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REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. G-044US04DIV
Patent No. 6,908,988

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Lydie Bougueleret
Issued	:	June 21, 2005
Patent No.	:	6,908,988
For	:	Nucleic Acid Encoding A Retinoblastoma Binding Protein (RBP-7) and Polymorphic Markers Associated with Said Nucleic Acid

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction (in duplicate) for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 5, line 61:	Page 7, line 7:
"T/EIA"	--T/E1A--
Column 16, line 26:	Page 20, line 3:
"consisting longest"	--consisting of the longest--

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Column 16, line 48:	Page 20, line 17:
"sites comprises"	--sites comprising--
Column 16, line 49:	Page 20, line 18:
"5896 and between"	--5896 and 5901 and between--
Column 16, line 57:	Page 20, line 24:
"Exons 2"	--Exon 2--
Column 20, line 53:	Page 26, line 7:
"exonuciease"	--exonuclease--
Column 28, line 41:	Page 36, line 8:
"VLSRPS™"	--VLSIPS™--
Column 31, line 3:	Page 39, line 12:
"SEQ ID) No."	--SEQ ID No.--
Column 45, line 59:	Page 57, lines 30-31:
"that at contains"	--that contains--
Column 47, line 42:	Page 60, line 3:
"Viasak"	--Vlasak--
Column 66, line 67:	Page 84, line 12:
"PBP-7"	--RBP-7--
Column 67, line 30:	Page 84, line 31:
"Expressions"	--Expression--
Column 73, line 27:	Page 92, line 4:
"as follows"	--as follows:--

Column 75, line 32:	Page 96, line 7:
"45284262"	--4528-4262--
Column 76, line 39:	Page 97, line 28:
"Stemberg"	--Sternberg--
Column 76, line 40:	Page 97, line 29:
"Stemberg"	--Sternberg--
Column 331, line 46:	Election Under 35 U.S.C. § 121 and Preliminary Amendment dated May 18, 2004 (original claim 53, numbered as new claim 4:
"anuno"	--amino--.

A true and correct copy of pages 7, 20, 26, 36, 39, 57, 60, 84, 92, 96, and 97 of the specification as filed and Applicants' Election Under 35 U.S.C. § 121 and Preliminary Amendment dated May 18, 2004 which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,

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FCE/sl
Attachments: Copy of pages 7, 20, 26, 36, 39, 57, 60, 84, 92, 96, and 97 of the specification as filed and Applicants' Election Under 35 U.S.C. § 121 and Preliminary Amendment

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catalytic subunit and several proteins designated generically as "Retinoblastoma Binding Proteins" (RBBP), some of these latter proteins being defined as E2F-like proteins.

Defeo-Jones et al. (1991) have cloned the cDNA of two members of the RBBP family, namely RBP-1 and RBP-2. RBP-1 and RBP-2 bind specifically to the RB protein *in vitro*. RBP-2 has been shown to interact noncovalently with RB ptotein via the binding of a consensus amino acid sequence of RBP-2, namely the LXCXE amino acid sequence, to the conserved T/E1A pocket of the RB protein (Kim et al., 1994). This LXCXE consensus amino acid sequence is also present within the adenovirus E1A protein, the SV40 large T antigen as well as within the human papillomavirus E7 protein. RBP-1 and RBP-2 have been hypothesized to function as transcription factors, like E2F. Helin et al. (1992) have cloned a cDNA encoding another member of the RBBP family, namely RBP-3. Sakai et al. (1995) have cloned a novel RBBP protein designated as RBP-6, the locus of which has been mapped on chromosome 16 between p11.2 and p12.

For the E2F family, replicating and differentiating cells need the RB protein or RB protein family members (e.g. p107 or p130) to counterbalance its apoptotic effect. E2F induces apoptosis when over-expressed in cells with the wild type p53 gene, but favors proliferation in p53 -/- cells. E2F-induced apoptosis follows entry of the cell into S-phase. The E2F death-promoting effect can be blocked by co-expression of p105, a RB protein family member. Conversely, by gene knock-out studies, it has been demonstrated that E2F is critical for the normal development of diverse cell types. Mice null for the E2F1 gene show defects at a young age in the terminal differentiation of cell types in which apoptosis play an important role, namely T-cells or epithelial cells of the testis or of other exocrine glands. With increasing age, these animals develop wide-spread tumors. This data indicates that E2F plays a physiological role in normal development, probably by inducing apoptosis in a specific set of developing cells.

The retinoblastoma binding proteins of the E2F type have also been described in PCT Application No. WO 65/24223, PCT Application No. WO 96/25494 and in US Patent No. 5,650,287, the disclosures of which are incorporated herein by reference in their entireties. Other retinoblastoma binding proteins have been described, notably in PCT Application No. WO 94/12521 , in PCT Application No. WO 95/17198, in PCT Application No. 93/23539 and in PCT Application No. WO 93/06168, the disclosures of which are incorporated herein by reference in their entireties.

DEFINITIONS

Before describing the invention in greater detail, the following definitions are set forth to illustrate and define the meaning and scope of the terms used to describe the invention herein.

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Exon	SEQ ID No.	Begining position in SEQ ID No. 1	End position In SEQ ID No. 1
12	16	103570	103642
13	17	105085	105179
14	18	106683	106780
15	19	107799	108042
16	20	108376	108551
17	21	114336	114593
18	22	132247	132331
19	23	134151	134349
20	24	145566	146774
21	25	150447	150560
22	26	152960	153175
23	27	155591	155737
24	28	159702	161451

The middle line depicts the main structural features of a purified or isolated nucleic acid consisting of the longest cDNA that is obtained after reverse transcribing a mRNA generated after transcription of the *RBP-7* gene. The longest mRNA has a nucleotide length of about 6 kilobases.

As it is depicted in Figure 1, the main characteristics of the longest *RBP-7* cDNA are the following :

a) A 5'-UTR region extending from the nucleotide at position 1 to the nucleotide at position 441 of SEQ ID No. 4;

b) An open reading frame (ORF) encoding the longest form of RBP-7 protein, wherein said ORF extends from the nucleotide at position 442 to the nucleotide at position 4380 of SEQ ID No. 4. The ATG translation start site is located between the nucleotide at position 442 and the nucleotide at position 444 of SEQ ID No. 4. The stop codon is located between the nucleotide at position 4378 and the nucleotide at position 4380 of SEQ ID No. 4.

c) A 3'-UTR region extending from the nucleotide at position 4381 to the nucleotide at position 6002 of SEQ ID No. 4. This 3'-UTR region contains four potential polyadenylation sites comprising respectively the nucleotides between positions 4878 and 4883, 5116 and 5121, 5896 and 5901 and between positions 5981 and 5986 of SEQ ID No. 4.

Figure 2 is a representation of the *RBP-7* gene in which the 24 exons are shown as closed boxes.

a) In each closed box that represents a given Exon, there are indicated both a number of base pairs corresponding to the non coding sequence eventually present in this Exon, and a number of amino acids. The number of amino acids is calculated as follows, starting from Exon 2 : Exon 2 contains two complete codons and the first base of a third codon; only the two

which will be detected when placed under the control of a biologically active derivative polynucleotide of SEQ ID No. 3.

Regulatory polynucleotides of the invention may be prepared from the nucleotide sequence of SEQ ID No. 1 or the sequences complementary thereto by cleavage using the suitable restriction enzymes, as described in Sambrook et al. (1989), supra.

Regulatory polynucleotides may also be prepared by digestion of the nucleotide sequence of SEQ ID No. 1 or the sequences complementary thereto by an exonuclease enzyme, such as Bal31 (Wabiko et al., 1986).

These regulatory polynucleotides can also be prepared by nucleic acid chemical synthesis, as described elsewhere in the specification, when oligonucleotide probes or primers synthesis is disclosed.

The regulatory polynucleotides according to the invention may advantageously be part of a recombinant expression vector that may be used to express a coding sequence in a desired host cell or host organism. The recombinant expression vectors according to the invention are described elsewhere in the specification.

The above defined polynucleotides that carry the expression and/or regulation signals of the *RBP-7* gene may be used, for example as part of a recombinant vector, in order to drive the expression of a desired polynucleotide, said desired polynucleotide being either (1) a polynucleotide encoding a RBP-7 protein, or a fragment or variant thereof, or (2) an "heterologous" polynucleotide, such as a polynucleotide encoding a desired "heterologous" polypeptide or a desired RNA in a recombinant cell host.

The invention also encompasses a polynucleotide comprising, consisting essentially of , or consisting of :

a) a nucleic acid comprising a regulatory polynucleotide of SEQ ID No. 2, or the sequence complementary thereto, or a biologically active fragment or variant thereof;

b) a polynucleotide encoding a desired polypeptide or nucleic acid.

c) Optionally, a nucleic acid comprising a regulatory polynucleotide of SEQ ID No. 3, or the sequence complementary thereto, or a biologically active fragment or variant thereof.

In a preferred embodiment, a polynucleotide such as disclosed above comprises the nucleic acid of SEQ ID No. 2, or the sequences complementary thereto, or a fragment, a variant or a biologically active derivative thereof which is located at the 5'end of the polynucleotide encoding the desired polypeptide or polynucleotide.

In another embodiment, a polynucleotide such as that above described comprises the nucleic acid of SEQ ID No. 3, or the sequence complementary thereto, or a fragment, a variant or a biologically active derivative thereof which is located at the 3' end of the polynucleotide

publications WO 90/15070 and 92/10092, the disclosures of which are incorporated herein by reference in their entireties. These arrays may generally be produced using mechanical synthesis methods or light directed synthesis methods which incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis (Fodor et al., Science, 251:767-777, 1991). The immobilization of arrays of oligonucleotides on solid supports has been rendered possible by the development of a technology generally identified as "Very Large Scale Immobilized Polymer Synthesis" (VLSIPS™) in which, typically, probes are immobilized in a high density array on a solid surface of a chip. Examples of VLSIPS™ technologies are provided in US Patents 5,143,854 and 5,412,087 and in PCT Publications WO 90/15070, WO 92/10092 and WO 95/11995, the disclosures of which are incorporated herein by reference in their entireties, which describe methods for forming oligonucleotide arrays through techniques such as light-directed synthesis techniques. In designing strategies aimed at providing arrays of nucleotides immobilized on solid supports, further presentation strategies were developed to order and display the oligonucleotide arrays on the chips in an attempt to maximize hybridization patterns and sequence information. Examples of such presentation strategies are disclosed in PCT Publications WO 94/12305, WO 94/11530, WO 97/29212 and WO 97/31256, the disclosures of which are incorporated herein by reference in their entireties.

In another embodiment of the oligonucleotide arrays of the invention, an oligonucleotide probe matrix may advantageously be used to detect mutations occurring in the *RBP-7* gene and in its regulatory region. For this particular purpose, probes are specifically designed to have a nucleotide sequence allowing their hybridization to the genes that carry known mutations (either by deletion, insertion of substitution of one or several nucleotides). By known mutations is meant mutations on the *RBP-7* gene that have been identified according, for example to the technique used by Huang et al. (1996) or Samson et al. (1996).

Another technique that is used to detect mutations in the *RBP-7* gene is the use of a high-density DNA array. Each oligonucleotide probe constituting a unit element of the high density DNA array is designed to match a specific subsequence of the *RBP-7* genomic DNA or cDNA. Thus, an array comprising, consisting essentially of, or consisting of oligonucleotides complementary to subsequences of the target gene sequence is used to determine the identity of the target sequence with the wild gene sequence, measure its amount, and detect differences between the target sequence and the reference wild gene sequence of the *RBP-7* gene. One such design, termed 4L tiled array, uses a set of four probes (A, C, G, T), preferably 15-nucleotide oligomers. In each set of four probes, the perfect complement will hybridize more strongly than mismatched probes. Consequently, a nucleic acid target of length L is scanned for mutations with a tiled array containing 4L probes, the whole probe set containing all the possible

further been described in several patents including US Patents 4,683,195, 4,683,202 and 4,965,188. Each of these publications is incorporated by reference.

One of the aspects of the present invention is a method for the amplification of the human *RBP-7* gene, particularly of the genomic sequences of SEQ ID No. 1 or of the cDNA sequence of SEQ ID No. 4, or a fragment or a variant thereof in a test sample, preferably using the PCR technology. The method comprises the steps of contacting a test sample suspected of containing the target *RBP-7* encoding sequence or portion thereof with amplification reaction reagents comprising a pair of amplification primers, and eventually in some instances a detection probe that can hybridize with an internal region of amplicon sequences to confirm that the desired amplification reaction has taken place.

Thus, the present invention also relates to a method for the amplification of a human *RBP-7* gene sequence, particularly of a portion of the genomic sequences of SEQ ID No. 1 or of the cDNA sequence of SEQ ID No. 4, or a variant thereof in a test sample, said method comprising the steps of :

a) contacting a test sample suspected of containing the targeted *RBP-7* gene sequence comprised in a nucleotide sequence selected from a group consisting of SEQ ID Nos 1 and 4, or fragments or variants thereof with amplification reaction reagents comprising a pair of amplification primers as described above and located on either side of the polynucleotide region to be amplified, and

b) optionally detecting the amplification products.

In a preferred embodiment of the above amplification method, the amplification product is detected by hybridization with a labeled probe having a sequence which is complementary to the amplified region.

The primers are more particularly characterized in that they have sufficient complementarity with any sequence of a strand of the genomic sequence close to the region to be amplified, for example with a non-coding sequence adjacent to exons to amplify.

In a particular embodiment of the invention, the primers are selected form the group consisting of the nucleotide sequences detailed in Table C below.

- establishing a statistically significant association between one allele of at least one marker and the trait.

Preferably, the trait positive and trait negative individuals are selected from non-overlapping phenotypes, at opposite ends of the non-bimodal phenotype spectra of the trait under study. In some embodiments, the biallelic marker is one of the biallelic markers of the present invention.

In a preferred embodiment, the trait is a disease and preferably a cancer.

The present invention also provides a method for the identification and characterization of an association between a haplotype comprising alleles for several biallelic markers of the human *RBP-7* gene and a trait. The method comprises the steps of :

- genotyping a group of biallelic markers according to the invention in trait positive and trait negative individuals; and

- establishing a statistically significant association between a haplotype and the trait.

In some embodiments, the haplotype comprises two or more biallelic markers defined in SEQ ID Nos 30-71.

The step of testing for and detecting the presence of DNA comprising specific alleles of a biallelic marker or a group of biallelic markers of the present invention can be carried out as described further below.

VECTORS FOR THE EXPRESSION OF A REGULATORY OR A CODING POLYNUCLEOTIDE ACCORDING TO THE INVENTION

Generally, a recombinant vector of the invention may comprise any of the polynucleotides described herein, including regulatory sequences, coding sequences and polynucleotide constructs, as well as any *RBP-7* primer or probe as defined above. More particularly, the recombinant vectors of the present invention can comprise any of the polynucleotides described in the "*RBP-7* Gene, Corresponding cDNAs And *RBP-7* Coding And Regulating Sequences" section, and the "Oligonucleotide Probes And Primers" section.

Any of the regulatory polynucleotides or the coding polynucleotides of the invention may be inserted into recombinant vectors for expression in a recombinant host cell or a recombinant host organism.

Thus, the present invention also encompasses a family of recombinant vectors that contains either a *RBP-7* regulatory polynucleotide or a *RBP-7* coding polynucleotide or both of them. Preferably, the present invention concerns recombinant vectors that contains either a *RBP-7* regulatory polynucleotide or a *RBP-7* coding polynucleotide comprising at least one of the biallelic markers of the invention, particularly those of SEQ ID Nos 30-71.

(Pharmingen) that is used to transfect the SF9 cell line (ATCC No. CRL 1711) which is derived from *Spodoptera frugiperda*. Other baculovirus vectors are described in Chai et al. (1993), Vlasak et al. (1983) and Lenhardt et al. (1996).

Mammalian expression vectors will comprise an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example SV40 origin, early promoter, enhancer, splice and polyadenylation sites may be used to provide the required nontranscribed genetic elements.

Large numbers of suitable vectors and promoters are known to those of skill in the art, and commercially available, such as bacterial vectors : pQE70, pQE60, pQE-9 (Qiagen), pbs, pD10, phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16A, pNH18A, pNH46A (Stratagene); ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia); or eukaryotic vectors : pWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene); pSVK3, pBPV, pMSG, pSVL (Pharmacia); baculovirus transfer vector pVL1392/1393 (Pharmingen); pQE-30 (QIAexpress).

Promoters

The suitable promoter regions used in the expression vectors according to the present invention are choosen taking into account of the cell host in which the heterologous gene has to be expressed.

Preferred bacterial promoters are the LacI, LacZ, the T3 or T7 bacteriophage RNA polymerase promoters, the polyhedrin promoter, or the p10 protein promoter from baculovirus (Kit Novagen) (Smith et al., 1983.; O'Reilly et al., 1992), the lambda P_R promoter or also the trc promoter.

Preferred promoters for the expression of the heterologous gene in eukaryotic hosts are the early promoter of CMV, the Herpes simplex virus thymidine kinase promoter, the early or the late promoter from SV40, the LTR regions of certain retroviruses or also the mouse metallothionein I promoter.

Promoter regions can be selected from any desired gene using, for example, CAT (chloramphenicol transferase) vectors and more preferably pKK232-8 and pCM7 vectors. Particularly named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda PR, PL and trp. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-L. Selection of a convenient vector and promoter is well within the level of ordinary skill in the art.

For the design of suitable recombinant vectors useful for performing the screening methods described above, it will be referred to the section of the present specification wherein the preferred recombinant vectors of the invention are detailed.

Using DNA recombination techniques well known by the one skill in the art, the RBP-7 protein encoding DNA sequence is inserted into an expression vector, downstream from its promoter sequence. As an illustrative example, the promoter sequence of the *RBP-7* gene is contained in the nucleic acid of SEQ ID No. 2.

The quantification of the expression of the RBP-7 protein may be realized either at the mRNA level or at the protein level. In the latter case, polyclonal or monoclonal antibodies may be used to quantify the amounts of the RBP-7 protein that have been produced, for example in an ELISA or a RIA assay.

In a preferred embodiment, the quantification of the RBP-7 mRNA is realized by a quantitative PCR amplification of the cDNA obtained by a reverse transcription of the total mRNA of the cultivated RBP-7-transfected host cell, using a pair of primers specific for *RBP-7*.

Expression levels and patterns of *RBP-7* may be analyzed by solution hybridization with long probes as described in International Patent Application No. WO 97/05277, the entire contents of which are incorporated herein by reference. Briefly, the *RBP-7* cDNA or the *RBP-7* genomic DNA described above, or fragments thereof, is inserted at a cloning site immediately downstream of a bacteriophage (T3, T7 or SP6) RNA polymerase promoter to produce antisense RNA. Preferably, the *RBP-7* insert comprises at least 100 or more consecutive nucleotides of the genomic DNA sequence or the cDNA sequences, particularly those comprising at least one of SEQ ID Nos 30-71 or those encoding mutated RBP-7. The plasmid is linearized and transcribed in the presence of ribonucleotides comprising modified ribonucleotides (i.e. biotin-UTP and DIG-UTP). An excess of this doubly labeled RNA is hybridized in solution with mRNA isolated from cells or tissues of interest. The hybridizations are performed under standard stringent conditions (40-50°C for 16 hours in an 80% formamide, 0.4 M NaCl buffer, pH 7-8). The unhybridized probe is removed by digestion with ribonucleases specific for single-stranded RNA (i.e. RNases CL3, T1, Phy M, U2 or A). The presence of the biotin-UTP modification enables capture of the hybrid on a microtitration plate coated with streptavidin. The presence of the DIG modification enables the hybrid to be detected and quantified by ELISA using an anti-DIG antibody coupled to alkaline phosphatase.

METHODS FOR INHIBITING THE EXPRESSION OF A *RBP-7* GENE

Other therapeutic compositions according to the present invention comprise advantageously an oligonucleotide fragment of the nucleic sequence of *RBP-7* as an antisense tool or a triple helix tool that inhibits the expression of the corresponding *RBP-7* gene.

TABLE 3

Marker Name	Mis. 1 in SEQ ID No.	Mis. 2 in SEQ ID No.
5-124-273	102	123
5-127-261	103	123
5-128-60	104	-
5-129-144	105	-
5-130-257	106	125
5-130-276	107	126
5-131-395	108	127
5-133-375	109	-
5-135-155	110	-
5-135-198	111	-
5-135-357	112	128
5-136-174	113	129
5-140-120	114	130
5-140-348	115	-
5-140-361	116	-
5-143-101	117	131
5-143-84	118	132
5-145-24	119	133
5-148-352	120	134
99-1437-325	121	135
99-1442-224	122	136

The microsequencing reaction was performed as follows :

After purification of the amplification products, the microsequencing reaction mixture was prepared by adding, in a 20µl final volume: 10 pmol microsequencing oligonucleotide, 1 U Thermosequenase (Amersham E79000G), 1.25 µl Thermosequenase buffer (260 mM Tris HCl pH 9.5, 65 mM $MgCl_2$), and the two appropriate fluorescent ddNTPs (Perkin Elmer, Dye Terminator Set 401095) complementary to the nucleotides at the polymorphic site of each biallelic marker tested, following the manufacturer's recommendations. After 4 minutes at 94°C, 20 PCR cycles of 15 sec at 55°C, 5 sec at 72°C, and 10 sec at 94°C were carried out in a Tetrad PTC-225 thermocycler (MJ Research). The unincorporated dye terminators were then removed by ethanol precipitation. Samples were finally resuspended in formamide-EDTA loading buffer and heated for 2 min at 95°C before being loaded on a polyacrylamide sequencing gel. The data were collected by an ABI PRISM 377 DNA sequencer and processed using the GENESCAN software (Perkin Elmer).

Following gel analysis, data were automatically processed with software that allows the determination of the alleles of biallelic markers present in each amplified fragment.

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I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office on May 18, 2004.

Frank C. Eisenschenk, Ph.D., Patent Attorney

ELECTION UNDER 35 U.S.C. § 121
AND PRELIMINARY AMENDMENT
Examining Group 1636
Patent Application
Docket No. G-044US04DIV
Serial No. 10/071,179

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Konstantina T. Katcheves
Art Unit	:	1636
Applicant	:	Lydie Bougueleret
Serial No.	:	10/071,179
Filed	:	March 19, 2002
Conf. No.	:	2980
For	:	Nucleic Acid Encoding A Retinoblastoma Binding Protein (RBP-7) and Polymorphic Markers Associated with Said Nucleic Acid

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

ELECTION UNDER 35 U.S.C. § 121 AND PRELIMINARY AMENDMENT

Sir:

A Petition and Fee for a one-month Extension of Time through and including May 19, 2004 accompanies this Election. In response to the written Restriction Requirement dated March 19, 2004 in the above-identified patent application, Applicant hereby elects to prosecute the invention of Group III (claim 30 and newly presented claims 31-64), without traverse.

Prior to examination, Applicant also respectfully requests that the subject application be amended as follows:

In the Claims

1-29 (canceled)

30 (currently amended). An isolated and purified polypeptide comprising ~~the~~ a contiguous span of at least six amino acids of SEQ ID ~~NO.~~NO: 29.

31 (new). The isolated and purified polypeptide according to claim 30, comprising a contiguous span of at least 40 amino acids of SEQ ID NO: 29.

32 (new). The isolated and purified polypeptide of claim 31, wherein said amino acids include position 293 of SEQ ID NO: 29 and wherein position 293 is aspartic acid.

33 (new). The isolated and purified polypeptide of claim 31, wherein said amino acids include position 293 of SEQ ID NO: 29 and wherein said 293 is glycine.

34 (new). The isolated and purified polypeptide of claim 31, wherein said amino acids include position 963 of SEQ ID NO: 29 and wherein position 963 is glycine.

35 (new). The isolated and purified polypeptide of claim 31, wherein said amino acids include position 963 of SEQ ID NO: 29 and wherein said position 963 is glutamic acid.

36 (new). The isolated and purified polypeptide of claim 31, wherein said amino acids include position 969 of SEQ ID NO: 29 and wherein position 969 is leucine.

37 (new). The isolated and purified polypeptide of claim 31, wherein said amino acids include position 969 of SEQ ID NO: 29 and wherein position 969 is methionine.

38 (new). An isolated and purified polypeptide comprising a fragment of the RBP-7 amino acid sequence of SEQ ID NO: 29, wherein said fragment is encoded by a polynucleotide sequence comprising SEQ ID NO: 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28.

39 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 5.

40 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 6.

41 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 7

42 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 8.

43 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 9.

44 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 10.

45 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 11.

46 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 12.

47 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 13.

48 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 14.

49 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 15.

50 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 16.

51 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 17.

52 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 18.

53 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 19.

54 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 20.

55 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 21.

56 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 22.

57 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 23.

58 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 24.

59 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 25.

60 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 26.

61 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 27.

62 (new). The isolated and purified polypeptide according to claim 38, comprising the RBP-7 amino acid sequence encoded by SEQ ID NO: 28.

63. (new). The isolated and purified polypeptide according to claim 30, wherein said polypeptide comprises SEQ ID NO: 29.

64. (new). The isolated and purified polypeptide according to claim 63, wherein said polypeptide is encoded by a polynucleotide comprising nucleotides 442 to 4377 of SEQ ID NO: 4.

Remarks

Claims 25, 27, 29, and 30 were pending in the subject application. In the most recent Office Action, a Restriction Requirement was issued in this matter. By way of the response of this date, Applicant has amended claim 30, canceled claims 25, 27, and 29, and added new claims 31-64. Support for the new claims and the amendments made to claim 30 can be found, for example, at page 14, lines 21-28, page 27, lines 20-26, and page 73, line 20 through page 76, line 5. Accordingly, claims 30-64 are currently before the Examiner. Favorable consideration of the claims in view of this response, and in view of the remarks set forth herein, is earnestly solicited.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Respectfully submitted,

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FCE/sl

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,908,988

APPLICATION NO.: 10/071,179

DATED : June 21, 2005

INVENTOR : Lydie Bougueleret

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5,
Line 61, "T/EIA" should read --T/E1A--.

Column 16,
Line 26, "consisting longest" should read --consisting of the longest--.
Line 48, "sites comprises" should read --sites comprising--.
Line 49, "5896 and between" should read --5896 and 5901 and between--.
Line 57, "Exons 2" should read --Exon 2--.

Column 20,
Line 53, "exonuciease" should read --exonuclease--.

Column 28,
Line 41, "VLSRPS™" should read --VLSIPS™--.

Column 31,
Line 3, "SEQ ID) No." should read --SEQ ID No.--.

Column 45,
Line 59, "that at contains" should read --that contains--.

Column 47,
Line 42, "Viasak" should read --Vlasak--.

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Column 66,
Line 67, "PBP-7" should read --"RBP-7--.

Column 67,
Line 30, "Expressions" should read --Expression--.

Column 73,
Line 27, "as follows" should read --as follows:--.

Column 75,
Line 32, "45284262" should read --4528-4262--.

Column 76,
Line 39, "Stemberg" should read --Sternberg--.
Line 40, "Stemberg" should read --Sternberg--.

Column 331,
Line 46, "anuno" should read --amino--.

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